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Four Years Later, Is It Already Known The Origin Of SARS-Cov-2?

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Abstract

Introduction: Although the quantity of scientific information about COVID-19 and SARS-CoV-2 (the coronavirus responsible for the COVID-19 pandemic) is currently enormous, covering a large number of topics, there are still some important gaps, being the origin of SARS-CoV-2 one of the most significant.

Objective: The current review was aimed at updating the available scientific data on the origin of SARS-CoV-2. It covers the period between the publication in 2022 of my previous review on that issue and December 31, 2023.

Methods: The databases PubMed and Scopus were used to collect the documents reviewed here. "Origin of SARS-CoV-2" was the search term. Those papers/articles considered as *background noises*, as well as those documents without scientific support, were not included in the review.

Results: In the present review, and similarly to the results of my two previous review articles (2021 and 2022) on the topic, there have not been significant scientific advances in the knowledge of the origin of SARS-CoV-2. The hypotheses of that origin are a zoonotic origin or a possible leak of this coronavirus from a laboratory. According to the reviewed papers, there is much greater scientific support for the first one.

Conclusion: The main gap in the zoonotic hypothesis is the lack of a detected intermediate host, which has not been found yet. In turn, although the hypothesis of a laboratory leak has not been supported by sufficient scientific evidence, it cannot be definitively discarded.

Keywords: SARS-CoV-2; Origin; Zoonosis; Laboratory Leak; COVID-19.

Introduction

In September 2021, I published a paper entitled "What we know and what we need to know about the origin of SARS-CoV-2", whose purpose was to review the scientific literature on the origin of SARS-CoV-2 published in journals indexed in PubMed and/or Scopus **[1]**. The review covered the period from January 1, 2020 to July 19, 2021, and it was aimed at assessing the two main possible origins for the SARS-CoV-2: natural (zoonotic) or unnatural (mainly laboratory) **[1]**. When that paper was being prepared, the available literature was certainly very scarce in comparison to the global information published at that time on SARS-CoV-2/COVID-19. Thus, PubMed included 1675 results on the "o*rigin of SARS-CoV-2*", but most of them might be considered as *background noises*, not being computable to establish/know that origin. A careful revision of the titles and abstracts of those 1675 documents showed that no more than 100 of them were more or less directly related to the real search term ("origin of SARS-CoV-2").

Moreover, a part of the documents found in the search were focused on discussions/debates about the potential origin of SARS-CoV-2, not being supported by sufficient scientific evidence. Therefore, they were not included in that review. A detailed analysis of the conclusions of the revised documents showed that the zoonotic hypothesis would be the most probable, with bats and pangolins being possibly the origin of the coronavirus. However, the intermediate species of SARS-CoV-2 was not confirmed yet. In contrast, I found that some researchers clearly pointed to an unnatural origin of SARS-CoV-2.

Notwithstanding, the conclusions of the documents involved in that potential origin were not strongly based on strict scientific evidence, being most of them largely speculative **[1]**. In 2022, I published a new review **[2]**, which was aimed at updating the information on the origin of SARS-CoV-2. That paper included the latest documents published from I finished the search for preparing my previous review (July 19, 2021) **[1]** until July 27, 2022. As expected, the information found for the second review was bigger than previously available. For example, 1675 and 2687 documents were found in PubMed on July 19, 2021, and July 27, 2022, respectively. Nevertheless, as already occurred when writing the first review **[1]**, most new documents were also considered as "*background noises*," being the real information on the specific origin of the coronavirus focused only on a reduced number of papers.

To date, the question of the origin(s) of COVID-19 remains still without having a conclusive answer **[3]**. Certainly, the theory of the zoonotic origin has -since a scientific point of view- much more followers than the unnatural origin (mainly focused on the laboratory origin). While the zoonotic hypothesis has received an important scientific support, the theory assuming that SARS-CoV-2 was deliberately engineered at the Wuhan Institute of Virology, and then, either inadvertently or otherwise, released to the public by a laboratory worker, does not seem to be sufficiently supported by scientific evidence **[4]**.

In order to adequately prevent and/or handle -in the best way possible- potential further pandemics caused by coronavirus, it is extraordinarily important to know which was the origin of SARS-CoV-2. Consequently, this has been again the purpose of the current review, aimed at collecting and updated the most recent data on the topic. For preparing the present review, the databases PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/) were used. The "origin of SARS-CoV-2" was once again the search term. For each category -zoonotic or other origins- the documents reviewed here are, in general, presented according to the dates of publication, from furthest to most recent. To establish what we really know and what science suggest could be the origin of SARS-CoV-2 have been the main goals of our previous articles **[1,2]** and also that of the current review.

Zoonotic origin of SARS-CoV-2

The genomic diversity of SARS-CoV-2 -early in the COVID-19 pandemic- was analyzed by Pekar et al. **[5]**. It was shown that SARS-CoV-2 genomic diversity before February 2020 probably comprised only two distinct viral lineages, which were denoted as "A" and "B." Using phylodynamic rooting methods, coupled with epidemic simulations, the authors observed that these lineages were the result of at least two separate cross-species transmission events into humans. Pekar et al. **[5]** concluded that the most probable explanation for the introduction of SARS-CoV-2 into humans would involve zoonotic jumps from undetermined, intermediate host animals at the Huanan market (Wuhan, China). On the other hand, the analyses carried out by Worobey et al. **[6]** also indicated that SARS-CoV-2 occurred through the live wildlife trade in China, being the Huanan market the epicenter of the COVID-19 pandemic. According to these authors, an explanation of the origin of the pandemic would be that live SARS-CoV-2-susceptible mammals would have been sold at that market, and within the market, SARS-CoV-2-positive environmental samples could have been spatially associated with individuals selling live mammals. Jiang and Wang **[7]** also reported that wildlife trade was probably the source of SARS-CoV-2. Multiple transmissions from wildlife at the Huanan market would have led to the diffusion of SARS-CoV-2.

With respect to the intermediate host for SARS-CoV-2, Gupta et al. **[8]** conducted a sequence comparative analysis of the host ACE2-interacting residues of the RBD of spike glycoprotein in SARS-CoV-2 isolates from bats, which were compared to the respective residues from pangolin isolated CoVs. These were collected from Guangdong province and Guangxi autonomous regions of South China. It was suggested that the Guangdong pangolins might be the intermediate hosts that adapted to SARS-CoV-2. They would represent a significant evolutionary link in the path of transmission of SARS-CoV-2. In the same line, in the conclusions of a review-paper on the SARS-CoV-2 origin, Gulati et al. **[9]** strongly supported the origin of SARS-CoV-2 in bats, being the transfer to humans occurring through the most probable evolutionary hosts: pangolins and minks. In a more general review covering the origin, host, and receptor of human coronaviruses **[10]**, the current understanding of seven human coronaviruses (229E, OC43, SARS, NL63, HKU1, MERS, and SARS-CoV-2) was examined. The potential host of wild animals of these coronaviruses was also discussed in relation to the origin of zoonotic diseases, including COVID-19. In this sense, Garry **[11,12]** was even more emphatic in relation to the origin of SARS-CoV-2. This author stated that no scientific data supported a laboratory leak of SARS-CoV-2. Therefore, the evidence was clear: SARS-CoV-2 emerged via the wildlife trade. The animal origin of SARS-CoV-2 was also supported by Zhao et al. **[13]**, who suggested that the most probable origin of SARS-CoV-2 might be pinpointed in Southeast Asia (Laos, Thailand, Cambodia and neighboring countries). These authors highlighted that coronaviruses with genomic sequences highly similar to SARS-CoV-2 had been found in those countries.

Interestingly, SARS-CoV-2 neutralizing antibodies were detected in Thai cave bats and a pangolin at a wildlife checkpoint in Southern Thailand. Regarding the epicenter of COVID-19 and the origin of the pandemic strain, Ruan et al. **[14]** suggested that a more accurate phrase/definition to establish the origin of COVID-19 would be 'somewhere, but probably not China.' It would be based on the evolutionary genetics of SARS-CoV-2 in the early phase of COVID-19 and the extensive attempts to find the 'smoking gun' in China's wildlife or the neighboring regions of SE Asia.

Hao et al. **[15]** also reviewed the scientific research that could be helpful to clarify the origin of SARS-CoV-2. These authors reviewed the pathogenesis, transmission, possible hosts, as well as the genome and protein structure of SARS-CoV-2. It was concluded that despite the fact that the animal host of SARS-CoV-2 had not yet been identified at the time of their review, the zoonotic origin was well supported by an important number of investigations. Based on the reviewed studies, the origin of SARS-CoV-2 would be very probably the result of a natural adaptation. However, Hao et al. **[15]** also noted that laboratory accidents could not be entirely ruled out. Similar conclusions were also reached in a systematic review -followed by a meta-analysis- conducted by Thakur et al. **[16]**, which was aimed at tracing and understanding the origin of SARS-CoV-2. It was observed that most authors considered the zoonotic spillover as the most probable origin of SARS-CoV-2, whereas the origin of SARS-CoV-2, based on laboratory spillover, would be unlikely according to the available information. In turn, the hypothesis called *Obscure Origin* by Thakur et al. **[16]**, which would include the *Frozen food theory*, was the subject of many criticisms and was considered unfounded.

In a review of the origin and evolution of SARS-CoV-2, Pagani et al. **[17]** concluded that this coronavirus, like all previous highly

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pathogenic human coronaviruses, had a zoonotic origin. It was noted that the previous SARS-CoV, which shares approximately 79% homology at the nucleotide sequence level with SARS-CoV-2, was linked to live animals sold in markets of Foshan (Guangdong Province, China). However, SARS-CoV-2 precise chain of animal-to-human transmission remained -at that time- undefined. In another article on the origin of SARS-CoV-2, Wu **[18]** reported the results of an updated analysis of the type IIS endonuclease maps in genomes of alpha-coronavirus, beta-coronavirus, and SARS-CoV-2. It was found that the restriction pattern was very diverse for alpha- and beta-coronaviruses, while the pattern of SARS-CoV-2 was not the only anomaly.

On the other hand, the BsamBI/*Bsa*I map in SARS-CoV-2 was dynamic, while new sites had emerged throughout the genome. According to Wu **[18]**, the scientific evidence would support the animal origin of SARS-CoV-2, potentially from genomic recombination events. An animal origin of SARS-CoV-2 was also suggested by Cohen **[19]**, who stated that genetic sequences from Wuhan market might point to animal that spread the coronavirus, although data remained hidden. Similarly, Mallapaty **[20]** suggested that although a progenitor of SARS-CoV-2 probably originated in bats, how it could pass to humans is not clear yet. In relation to this, Raccoon dogs, bamboo rats, and palm civets are some of the animals whose DNA has been found in swabs taken from the Huanan seafood market of Wuhan, which was -from the beginning- linked to the origin of the COVID-19 pandemic. The hypothesis that bats, probably via an intermediate animal (not yet identified), were the origin of SARS-CoV-2 was also supported by Dwyer **[21]**.

On the other hand, it has been shown that MpCoV-GX and MpCoV-GD efficiently utilize human ACE2 as the receptor. In turn, it has also been demonstrated in hamsters that MpCoV-GX exhibits infection characteristics similar to SARS-CoV-2 and direct contact transmissibility. Based on this, Liu et al. **[22]** investigated in wild-type BALB/c mice, human angiotensin-converting enzyme 2 (ACE2)-transgenic mice, and human ACE2 knock-in mice, the biological features of a SARSr-CoV-2 (SARS-CoV-2 related coronavirus) strain isolated from a smuggled Malayan pangolin. The results suggested that SARSr-CoV-2 virus from pangolins had the potential for interspecies infection. However, its pathogenicity was mild in mice.

In order to understand the origins of the SARS-CoV-2 pandemic, Yang et al. **[23]** investigated the deep phylogenetic relationships across gene trees by means of a consensus species tree, which was reconstructed from the eleven gene trees with their unique evolutionary histories. It was hypothesized that the species tree would permit inference about the origin of SARS-CoV-2 from animal reservoirs. The species coalescent indicated possible bat and pangolin origins of the SARS-CoV-2 pandemic. During the early stages of the COVID-19 outbreak, and for the surveillance of SARS-CoV-2 at the Huanan seafood market from January 1, 2020 and after the closure of the market, Liu et al. **[24]** collected 923 environmental samples, while from January 18, 2020, 457 samples of 18 species of animals were also collected. These samples consisted of unsold contents of refrigerators and freezers, swabs from stray animals, as well as the content of a fish tank. Using RT-qPCR, the authors detected SARS-CoV-2 in 73 environmental samples. However, none was detected in the animal samples. Three live viruses were successfully isolated, which shared nucleotide identity 99.99-100% with the human isolate HCoV-19/Wuhan/IVDC-HB-01/2019.

Moreover, SARS-CoV-2 lineage A (8782T and 28144C) was found in an environmental sample. The data reported by Liu et al. **[24]** were subsequently analyzed by Crits-Christoph et al. **[25]** using multiple novel genomic approaches. This analysis provided the genetic basis for a short list of potential intermediate hosts of SARS-CoV-2. Wildlife DNA was identified in all SARS-CoV-2 positive samples. It included species such as civets, bamboo rats, porcupines, hedgehogs, as well as raccoon dogs, a species known to be capable of SARS-CoV-2 transmission. Other animal viruses that might infect raccoon dogs, civets, and bamboo rats were also detected.

In a review regarding zoonosis and its relationship with the COVID-19 pandemic, Sánchez et al. **[26]** remarked that the pandemic made evident the importance of human interactions with other animals and ecosystems. Taking into account that the main determinants of the emergence of zoonoses are of anthropic origin, the authors highlighted the need of incorporating a multidisciplinary health vision into global decision-making. In relation to this, a knowledge of the natural evolution of zoonoses should make it possible to identify the critical points for their control. It should make also possible to identify potential candidate agents to cause future -and probably unavoidable- pandemics. In turn, in a recent review on the controversy of the zoonotic origin of SARS-CoV-2 and the risks of severity of reinfection and management of COVID-19, Chala et al. **[27]** concluded stating that although it is widely accepted that SARS-CoV-2 originated from animals, the exact source and transmission pathway remained unclear, being the origin of the COVID-19 virus still a topic of controversy.

Potential origins of SARS-CoV-2 other than zoonosis

At the beginning of the pandemic, Rahalkar and Bahulikar **[28]** suggested a potential link between the Mojiang (Yunnan, China) mine incident, which occurred in 2012, and the origin of SARS-CoV-2. It was based on the facts in the mineshaft in Mojiang, where a lethal pneumonia-like disease occurred in six miners, and a diverse group of coronaviruses was discovered in the mine following the outbreak. However, taking into account the clinical reports of that incident, Frutos et al. **[29]** stated that the Mojiang miners did not develop COVID-19, not being infected by SARS-CoV-2. According to these authors, there was no evidence supporting the Mojiang mine origin of SARS-CoV-2, as well as any of the laboratory leak theories. Notwithstanding, a number of flaws in the interpretation and analysis of Frutos et al. **[29]** were suggested by Rahalkar and Bahulikar **[30]**,

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who did not fully discard a laboratory origin of the coronavirus. Directly related with this debate, Frutos et al. **[31,32]** stated that there is not determined origin to viruses, including also SARS-CoV-2. They suggested that there is simply an evolutionary and selective process in which chance and environment play a key role. Viruses circulate from host to host, animals or humans. Thus, pandemic viruses such as SARS-CoV-2 were already circulating in humans and evolving before the onset of disease (COVID-19).

Coccia **[33]** conducted a meta-analysis aimed at clarifying, whenever possible, likely sources of SARS-CoV-2. These sources included the possibility of a natural spillover or a laboratory accident as a potential consequence of scientific research. According to Coccia **[33]**, the results of the meta-analysis suggested that the natural spillover of new coronaviruses such as SARS-CoV-2, which have generated millions of deaths worldwide, has a remote probability of occurrence. By contrast, the origin of a hazardous viral agent associated with an accident of lab during scientific research would have a higher average probability of occurrence. In turn, although Leifels et al. **[34]** recognized that an estimated 75% of all emerging virus-associated infectious diseases possess a zoonotic origin, they also highlighted the importance of environmental factors concerning interactions between animals, pathogens and/or humans that drive the emergence of zoonoses. Dwyer **[21]** remarked that the hypothesis of accidental/deliberate laboratory leak, or virus present in frozen foods, has not sufficient scientific evidence to justify the unnatural origin of SARS-CoV-2.

In contrast, Bruttel et al. **[35]** observed that the synthetic fingerprint of SARS-CoV-2 was anomalous in wild coronaviruses, whereas it was common in lab-assembled viruses. The type of mutations that differentiate the restriction sites in SARS-CoV-2 are characteristic of engineering, while the concentration of silent mutations in the restriction sites would be very unlikely to have arisen by random evolution. Therefore, taking into account that the restriction site fingerprint and the pattern of mutations generating them would be extremely unlikely in wild coronaviruses but nearly universal in synthetic viruses, Bruttel et al. **[35]** strongly suggested a synthetic origin of SARS-CoV-2.

Yang et al. **[36]** argued that the spillover risk of bat CoVs could be evaluated by testing how viruses break through key human genetic barriers, including receptors, replication, as well as host defense, in an integrated framework. These researchers established an integrated framework and compared the zoonotic risk of human SARS-CoV-2, bat-derived WIV1-CoV, and pangolin-derived PCoV-GX. These are representative human and animal SARSr-CoVs, which use the human ACE2 receptor. The results showed that the pre-emergent bat BtCoV-WIV1 and pangolin PCoV-GX were less adapted to humans than SARS-CoV-2. It would suggest that it might be extremely rare for animal SARSr-CoVs to break all bottlenecks and cause successful zoonoses. In summary, the risk posed by SARS-related coronaviruses from both bat and pangolin would be low. In an interesting article by Berche **[37]**, entitled "Gain-of-function and origin of COVID-19", the information on the main two scenarios related with the origin of SARS-CoV-2 was reviewed. The hypothesis that the natural origin suggesting that a bat virus might directly have infected humans, spreading silently at low level for years, would not explain the origin in Wuhan, which is far away of natural virus reservoirs. An alternative would be the existence of an intermediate host, but to date, it has not been detected yet. Another potential scenario would be a laboratory accident after gain-of-function manipulations from a SARS-like virus. The occurrence of a human contamination by a natural CoV virus grown on cells in Wuhan cannot be discarded. On the other hand, Zapatero-Gaviria and Barba-Martin **[38]** published an article whose purpose was review the two main hypothesis on the origin of SARS-CoV-2: as a virus of zoonotic origin, or alternatively, as a leak from the high-level biosafety laboratory in Wuhan. It was concluded that three fundamental questions were not yet responded: 1) where did the virus come from?, 2) what was the intermediate animal host? and 3) why has the virus genome not been reproduced 100% in any coronaviruses found in bats? In an Editorial of the Journal of Virology, Alwine et al. **[39]** made a critical analysis of four hypotheses raised to explain the origin of SARS-CoV-2. These 4 hypotheses were the following: 1) SARS-CoV-2 arose from a laboratory-adapted CoV, 2) SARS-CoV-2 is a laboratory-constructed virus, 3) SARS-CoV-2 is a bat zoonosis in the human population, and 4) the SARS-CoV-2 origin is suggested by early cases in the COVID-19 outbreak. After a careful evaluation of the background and evidences of each of the 4 hypotheses, the authors -based on the current scientific data- concluded that hypotheses 1 and 2 were unlikely, while hypotheses 3 and 4 could not be ruled out by existing evidence. Thus, the lab leak and the zoonotic-origin explanations would not be equally probable, whereas the available evidence would favor the latter. In contrast, Lloyd et al. **[40]** recently concluded that SARS-CoV-2 might have been produced in a laboratory through well-established, widely available, and relatively simple techniques without needing sophisticated gain-of-function technology. The laboratory origin of SARS-CoV-2 would be reinforced by the highly significant association between a lower prevalence of specific genetic blood markers in East and South Asian populations -and lower mortality- in comparison with Western Europeans during comparable periods of the first wave of COVID-19. At that time, viral diversity and immunity induced by natural infection and/or vaccination might not have influenced outcomes.

Discussion

The scientific documents on the origin of SARS-CoV-2, published between July 27, 2022, and December 31, 2023, have been reviewed here. Not at all, this review has entered into conspiracy theories in which some people have suggested that SARS-CoV-2 might have been a biological weapon, released by some specific country, a country which would depend on their political leanings.

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To begin with, I would like to highlight that the number of available scientific documents regarding COVID-19 and/or SARS-CoV-2 is currently extraordinarily high. For example, on January 1, 2024, nothing more and nothing less than 404,778 results were found in PubMed when COVID-19 was used as the search term. In turn, using SARS-CoV-2, the number of results was 216,174, being 3,459 the documents found in that databases when the search term was specifically "origin of SARS-CoV-2". Therefore, it cannot be said that the scientific literature regarding SARS-CoV-2 is currently being limited/scarce. On the contrary, it is certainly spectacular. However, I had not been able of founding significant novelties with respect to my two previous reviews on the same topic **[1,2]**. According to the information reviewed in the current paper, the two initial hypothesis on the origin of SARS-CoV-2 (zoonotic and unnatural) remains still completely open, but with a very clear preponderance right now in favor of the zoonotic origin. Anyhow, and as also indicated in my previous reviews **[1,2]**, the only real fact is that there is not yet a definitive and well demonstrated scientific theory on the origin of SARS-CoV-2. An important gap in the prevailing theory is the lack of an essential intermediate host, which has not been found yet, while the hypothesis of a laboratory leak has not been supported by sufficient scientific evidence.

Nevertheless, it cannot be definitively discarded. As suggested by many scientists, and I absolutely agree, the search for the origin of SARS-CoV-2 is basic. It is if the world wants to be prepared to prevent/to respond to further potential coronavirus pandemics, which, unfortunately, probably will be unavoidable.

Conclusion

Based on the above reviewed documents, one of the main gaps regarding the zoonotic hypothesis is the lack of a well-established intermediate host. However, pangolin and minks -among other species- have been suggested as possible intermediate hosts. On the other hand, although the hypothesis of a laboratory leak has not been sufficiently supported by scientific evidences, it cannot be definitively discarded.

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